Prion Disease Overview
What is a prion?

- protein and infectious
- -ion (infectious, e.g. virion)
- No nucleic acid (e.g., DNA, RNA, “building blocks of life”)
- Non-degradable by typical sterilization
PrP: prion protein
PrP^C: normal prion protein (c=cellular)
PrP^Sc: disease causing protein (Sc=scrapie)

Animals

- Scrapie: sheet & goat
- Bovine spongiform encephalopathy (BSE): cow
- Chronic wasting disease (CWD): deer, elk, moose, caribou
Etiologies

- Genetic CJD
- Fatal familial insomnia
- Gerstmann-Sträussler-Scheinker

- Kuru
- Iatrogenic CJD
- Variant CJD
Age & Survival

• Age at disease onset
  – sCJD: mid to late life
  – genetic prion disease: mid to late life
  – variant CJD: young adulthood and mid life

• Duration
  – sCJD: 4-6 months on average, 25% live > 1 year
  – genetic prion disease: generally longer than sCJD, but varies widely by mutation (e.g., GSS)
  – vCJD: generally over a year
Epidemiology

• 1-2 new cases per million individuals per year across the entire population (all ages)
• 1/10,000 US deaths per year
• OH=10.5 million people
  – 10.5 new cases/yr
  – ~2.5 cases living past one year
  – Would not be unusual to have 13 active cases in OH

Definite Diagnosis - Neuropathology

H & E Staining (spongiform changes)

Immunohistochemistry (abnormal prion protein)
Probable sCJD

At least two clinical signs with dementia:
1. Myoclonus (e.g., twitches)
2. Cerebellar or visual symptoms (e.g., “drunken” walking, incoordination, depth misperception)
3. Pyramidal or extrapyramidal symptoms (e.g., weakness, tremors, Parkinson’s disease like walking)
4. Akinetic mutism (lack of voluntary speech & movement)

At least one of the following:
1. Periodic sharp wave complexes on electroencephalogram (EEG) (looks at brain waves)
2. 14-3-3 in spinal fluid and disease duration < 2 years
3. Abnormal findings in basal ganglia or at least two cortical (e.g., outside) regions on specific sequences on brain MRI

Electroencephalogram (EEG)

Periodic sharp wave complexes
Brain MRI

cortex

basal ganglia
Real-Time Quaking-Induced Conversion (RT-QuIC)

- Sample

PrPSc → ThT

PrPSc, PrPSc, PrPSc → ThT

PrPSc, PrPSc, PrPSc
# Genetic Prion Disease

## Table 1  Variations in the human prion protein gene coding region

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Mutation</th>
<th>Insertional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silent</td>
<td>Influential</td>
<td>Point</td>
</tr>
<tr>
<td>P68P</td>
<td>M129V</td>
<td>P102L</td>
</tr>
<tr>
<td>A117A</td>
<td>N171S?</td>
<td>P105L</td>
</tr>
<tr>
<td>G124G</td>
<td>E219K?</td>
<td>A117V</td>
</tr>
<tr>
<td>V161V</td>
<td>24bp deletion?</td>
<td>G131V</td>
</tr>
<tr>
<td>N173N*</td>
<td>I138M*</td>
<td>F198S</td>
</tr>
<tr>
<td>H177H</td>
<td>G142S*</td>
<td>E196K</td>
</tr>
<tr>
<td>T188T*</td>
<td>Y145s</td>
<td>E200K</td>
</tr>
<tr>
<td>D202D</td>
<td>Q160s</td>
<td>D202N</td>
</tr>
<tr>
<td>Q212Q</td>
<td>D178N–129V</td>
<td>V180I</td>
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<tr>
<td>R228R</td>
<td>D178N–129M</td>
<td>V210I</td>
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<tr>
<td>S230S</td>
<td>V180I</td>
<td>E211Q</td>
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<tr>
<td></td>
<td>V180I + M232R</td>
<td>Q217R</td>
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<tr>
<td></td>
<td>T183A</td>
<td>M232R</td>
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<tr>
<td></td>
<td>H187R</td>
<td>M232T</td>
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<tr>
<td></td>
<td>T188R</td>
<td>P238S</td>
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</tbody>
</table>

(Bold indicates CJD phenotype, underlined indicates GSS, italics indicate FFI. Others are not categorised, as the published data are insufficient, or findings are unusual to the known disease subtypes. *Referred from: [http://www.mad-cow.org/prion_point_mutations.html](http://www.mad-cow.org/prion_point_mutations.html)*)

Kovács GG, J Neurol 2002
Acquired Prion Disease

• Kuru
• Iatrogenic CJD (iCJD)
• Variant CJD (vCJD)
Kuru
Iatrogenic CJD

Two criteria for acquired prion disease*:
1) Taken from central nervous system
2) Placed in central nervous system, injected into body, or ingested

*Only vCJD has been transmitted by blood transfusions

Brown P, Neurology 2006
# VARIANT CREUTZFELDT-JAKOB DISEASE
## CURRENT DATA (FEBRUARY 2015)

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>TOTAL NUMBER OF PRIMARY CASES (NUMBER ALIVE)</th>
<th>TOTAL NUMBER OF SECONDARY CASES: BLOOD TRANSFUSION (NUMBER ALIVE)</th>
<th>RESIDENCE IN UK &gt; 6 MONTHS DURING PERIOD 1980-1996</th>
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<tbody>
<tr>
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<td>174 (0)</td>
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<tr>
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<td>4† (0)</td>
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<tr>
<td>Taiwan</td>
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<td>-</td>
<td>1</td>
</tr>
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</table>

† The third US patient with vCJD was born and raised in Saudi Arabia and has lived permanently in the United States since late 2005. According to the US case-report, the patient was most likely infected as a child when living in Saudi Arabia.

In the fourth US patient “the history... including extensive travel to Europe and the Middle East, supports the likelihood that infection occurred outside USA”

* The case from Japan had resided in the UK for 24 days in the period 1980-1996.
sCJD subtypes

A. Polymorphism (differences in code) at position 129 of the prion protein gene (MM, MV, or VV)
B. Prion protein type (differ by size/weight) (1, 2, or VPSPr)

sCJD subtype = A + B (MM1, VV2, etc)

Subtypes vary in neuropathology and clinical characteristics.